EXPERIMENTAL IMMUNITY WITH REFERENCE TO THE LEPROSY BACILLUS.*

PART II.†

A STUDY OF THE FACTORS DETERMINING THE CURE OF INDIVIDUALS INFECTED BY THE BACILLUS LEPRAE.

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The foundation for the horror and fear in which leprosy is held by the laity and also to a less marked degree by the medical profession depends chiefly on the popular belief in the absolute incurability of the disease. If it be possible to remove from leprosy the stigma of incurability and the corollary of ultimate fatality the disease will be relegated to a much less important place in sociologic, economic, and medical literature than tuberculosis and syphilis. Theoretically, it is difficult to conceive of any bacterial disease being incurable; there are, too, on record a sufficient number of well-attested cases of undoubted leprosy which have recovered and remained well to prove that under certain conditions cure of the disease may take place. Isadore Dyer[1] among others has published records of a number of cases where the infection has been eradicated by our present methods of treatment and regimen.

Among animals susceptible to both local and generalized lesions there is undoubtedly present some mechanism of defense, as the result of which the bacilli are unable to live indefinitely in their tissues. The protocols of monkeys, mice, goats, and guinea-pigs which have shown, a few months after a more or less fulminant infection, absolutely no signs of the disease either macroscopically or microscopically could be cited as evidence of the capacity of the animal tissues to eradicate the bacilli.

During the past eighteen months we have carried out several series of experiments in the hope of finding some clue which might

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[1] *Medical News*, 1905, 68, p. 230.

lead to the discovery of the manner in which the protective substances act and what they are, and, if possible, of procuring some means for increasing the potency and rapidity of development of such bodies as might be employed in the treatment of human leprosy. We have demonstrated[1] that the ordinary antibodies, such as agglutinins, amboceptors, etc., may be induced in animals by the injection of dead bacilli. In no instance, however, has it been possible to produce these bodies in similar proportions to those developed experimentally with many other bacteria nor has it been possible to protect animals against subsequent infection by means of preliminary injections of the dead organisms.

As stated in a former publication,[2] most animals, though more or less readily infected with leprosy bacilli, recover in a comparatively short time even when the percentage of antibodies present in their serum at the time of recovery is low. Such animals, moreover, are susceptible to reinfection after their recovery from a primary infection; this observation suggests that some mechanism other than the commonly considered immune bodies is active in the cure of the disease. It appears, therefore, that among animals the cause of the recovery from infection is rather the result of the inability of the bacillus to prolong its existence in the host than due to the development of any active protective process on the part of the infected animal. It is reasonable to suppose that protection is afforded the microorganism by the proliferation of cells of the epithelioid type and that with the disappearance of such cells and the exposure of the bacilli to the action of the tissue juices they are destroyed.

The results of our experiments demonstrate that although under ordinary conditions the leprosy bacillus is able to prolong indefinitely its existence in the human tissues, it is possible for the polymorphonuclear leukocytes to digest and destroy it. Normally, however, the pus cells only infrequently attack the organisms. The alteration in conditions necessary to bring about such reaction appears to be one affecting the bacteria themselves. We do not believe that this change is of the nature of an opsonic reaction, but rather is the result of the bacilli becoming more toxic and thus

[1] *Jour. Exper. Med.*, 1911, 14, p. 100. [2] *Loc. cit.*

stimulating polymorphonuclear activity. This increased toxicity seems to be due to a hypersensitiveness of the individual which results in an anaphylactic toxicity.

Although animals infected with the leprosy bacillus usually recover spontaneously in a comparatively short time and for this reason it is practically useless to attempt to test the therapeutic value of any procedure upon them, certain observations are of sufficient interest and importance to justify mention here.

Normal monkeys and guinea-pigs, when inoculated subcutaneously with living or dead leprosy bacilli, either do not react or show merely the development of a small area of hyperemia and edema accompanied by a proliferation of lymphoid, plasma, and epithelioid cells. As mentioned in a former publication,[1] there usually develops in animals previously sensitized to the bacilli a more extensive lesion which persists over a longer period and shows, if viable bacilli have been employed, a greater tendency to metastasis. In a certain percentage of animals, however, and this has been noted more especially in two monkeys which had recovered from a severe leprosy infection, an interesting and important phenomenon was observed. The reaction in these animals occurred in the following manner. Within 24 hours after the inoculation of one billion dead bacilli, there developed at the site of inoculation a somewhat reddened and apparently painful swelling which gradually increased in size, became softer, and about the third to fifth day fluctuated. Microscopically, the content of the mass was composed almost entirely of polymorphonuclear leukocytes, many of which had taken up the leprosy bacilli.

Among other animals we have observed similar reactions following second or third inoculations. This was especially noted in a horse inoculated in an effort to procure an antiserum. This animal received a primary dose of approximately two billion dead bacilli. Four days after the injection there developed at the site of inoculation a firm, raised mass nine centimeters in diameter, which gradually subsided and had practically disappeared at the end of one week. Following the second and third injections of live bacilli there promptly appeared a raised, tender mass beneath the

[1] *Jour. Exper. Med.*, 1911, 14, p. 100.

skin which rapidly increased in size and spontaneously ruptured on the fifth day. The contents consisted chiefly of pus cells, many of which contained the acid-fast bacilli. Moreover, the injections produced a leukocytosis of 10–20 thousand.

It is thus seen that under certain conditions the introduction of leprosy bacilli into the sensitized animal is characterized not only by the accumulation of polymorphonuclear leukocytes to the point of inoculation, but also an increase of these cells in the general circulation. It is also noted that the pus cells are capable of taking up the bacilli. The factors determining the accumulation of pus cells appear to be a condition of hypersensitiveness of the animal to the bacillus as a result of which the bacilli stimulate the activity of these cells.

The results of animal experiments lead us to think that if it is possible to increase the sensitiveness of the 'eper to the protein constituent of the leprosy bacillus which will result in a marked tissue reaction, an activity on the part of the polymorphonuclear leukocytes may be stimulated which will bring about the destruction of the bacilli throughout the human organism. That it is possible to promote a marked alteration in the reaction of the human tissues to the bacilli the following cases prove.

In New Orleans and at the Louisiana Lepers' Home several human cases of leprosy were selected for experimental treatment with killed cultures or with the protein extract of *B. leprae*. The cases for the most part were of the mixed type and represented active phases of the disease. Some of the incipient cases were of the maculo-anesthetic type, while others presented distinct tubercles and nerve lesions. Four of the patients, previous to the initiation of bacillary inoculations, had been under routine treatment with strychnine or Chaulmogra oil or Aesenic for varying periods with negative results.

Though the treatment of human cases with bacterio-protein is still in the experimental stage and no positive statement regarding a permanent cure can be made at this time, we are justified in reporting on the progress thus far reached with its use. Suffice it to say that the proper administration of large doses of the protein constituent of *B. leprae* in early cases of human leprosy produces

a distinct and marked improvement in the patient's condition and in certain cases causes a complete disappearance of all signs and symptoms of the disease. Whether in these apparently cured cases the results are permanent time only can determine, as not infrequently there is a disappearance of all external lesions for months in the natural course of the disease.

Whitmore and Clegg[1] report negative results from the treatment of 32 cases of human leprosy in which they used a glycerin extract and soap solution of killed leprosy cultures. These authors conclude that no benefit was noticeable in any of their cases though the patients were under treatment for a period of twelve and one-half months. Since our results with the bacillary products in the treatment of leprosy do not accord with theirs, we believe the difference is explained by the fact that their dosage was too small and its administration discontinued when a severe constitutional reaction followed the injections. In our experience a constitutional reaction is highly essential and to be desired. The more severe the reaction induced by the injection, the more marked is the subsequent improvement in the patient's condition.

CASE 1. A. F., 48 years of age, a man of large frame and comparatively stout. The diagnosis of leprosy was made one year before the institution of treatment although he stated that for four or five years previous he had noticed blotches appearing in his skin. During the past year he had worked only occasionally, his working time having been irregular during the latter months. He gave as the explanation a general weakness more particularly of the left hand which interfered with his grasping objects firmly. In December, 1910, he came under our observation, at this time unable to work and presenting very extensive lesions of leprosy. Practically his whole body was covered with large, firm, irregular, slightly raised, somewhat edematous, copper-colored patches. In several places, more especially over the forearm and back, these patches were from 0.5 to 2.5 cm. in the longest diameter.

The left ulnar nerve was palpable, there was almost complete analgesia and loss of power over the area of its distribution. The right hand was also numb and weak. Leprosy bacilli were found in great numbers in material from the tubercles and macules, none, however, were found in secretion from the nose. Leukocytes numbered 8,400, polymorphonuclear leukocytes, 67 per cent. A positive Wassermann and leprosy binding reaction was obtained. No agglutinins were found in dilution of 1 to 20.

Treatment by means of subcutaneous injections of bacilli killed by tricresol was instituted, December 20, 1910. The first injection consisted of four million bacilli. Treatment has been continued weekly from this time up to the present. Doses have

[1] *Philippine Jour. Sci.*, 1910, 5, p. 559.

been increased rapidly so that by March the patient was getting 2,000 million organisms at a time and since then the dose had gradually been increased up to six billion bacilli.

For the first two months although the patient claimed to feel better no objective evidence of improvement other than an increased power in the left hand was noted. During March, however, the patient's nerve lesions improved rapidly so that, according to his statement, he returned to work with complete return of power of grip.

Very soon after large doses of bacilli (over two billion) were used, it was noted that at the point of injection the day following the inoculation there appeared a firm swelling about 2.5 cm. in diameter having a reddened center and being moderately painful.

Simultaneously with the appearance of the local reactions at the site of injection it was noted that following each dose there developed in a larger or smaller number of lesions, especially those of the tubercular type situated upon the arms, an acute inflammatory reaction characterized by swelling, redness, edema, and the aggregation of polymorphonuclear leukocytes as shown by incision. These reactions appeared constantly after their beginning, for the most part different areas being involved each week, and in general the more advanced lesions showing a greater tendency to react. The first appearance of redness was evident about 18 to 24 hours after the injection. The manifestation continued to increase to the third or fourth day, gradually receding so that by the end of the week practically all edema had disappeared, and the lesions were characterized merely by a slight swelling and moderate redness. By the end of the third week after such an exacerbation not only was all evidence of the acute condition past but no leprous lesion was evident, a soft, more or less pigmented area alone remaining. In many of these "healed" areas, moreover, it was impossible to demonstrate the presence of bacilli.

As a rule, the patient complained of fever and malaise for two or three days following each injection. Upon several occasions when he was asked to return for observation his temperatures varied from 99.4° to 100.4°, 18 hours after the dose was given.

Coincidentally with the rise in temperature and reddening of the lesion a leukocytosis of from 10 to 14 thousand has been noted with a differential count of from 79 per cent to 76 per cent polymorphonuclear leukocytes. Recently the patient's blood has contained never less than 10,000 white cells, this number being found several days after inoculation. Following each injection the count rises to about 13,000 at the end of 24 hours, and to 14,000 or 15,000, 48 hours after the administration of the vaccine. From this time the number gradually falls, reaching 10,000 by the seventh day. This increase is found by differential count to consist chiefly of polymorphonuclear neutrophilic leukocytes.

At present the patient presents a definite and marked case of leprosy, but the distribution and evident activity of the lesions, especially the tubercular forms, have markedly diminished and all evidence of nerve involvement has disappeared. The lesions all over the body are less firm and the skin is softer and more pliable. The patient claims, too, to feel much stronger generally, excepting on those days when he suffers from fever.

Results of treatment: marked improvement and disappearance of all active lesions.

CASE 2. L. P., Spaniard, aged 36. A case of incipient leprosy, probably of four months' standing. Patient exceedingly well developed and nourished; fisherman by

occupation. Born in Louisiana. Presented himself at the Touro Infirmary, February 12, 1911, complaining of numbness of both lower extremities and more or less severe pain (rheumatoid in character) in the arms and legs. His chief trouble was the inability to use his left foot. He also complained of "feeling bad" and unfit for work.

On examination it was found that he had complete foot drop (left) and in places analgesic areas in the outer side of the left leg from the knee to the toes which corresponded very closely to the distribution of the peroneal nerve. There was a trophic ulcer approximately one centimeter in diameter on the outer side of the left toe. On the left buttock just above the gluteal fold there was a sharply defined elevated purplish red area measuring four centimeters in diameter. Deep incision of this area caused no pain. The normal skin immediately around this macule was hypersensitive. Smears prepared and stained from the bloody serum obtained by incising the macule showed innumerable acid-fast bacilli which corresponded morphologically and culturally to *B. lepra*. The bacilli occurred for the most part in dense colony masses within mononucleated cells. No polymorphonuclear leukocytes were demonstrable in the smears prepared from the serum free from blood.

A careful examination of the patient showed no other macular skin lesion except on the face, which was swollen and of a purplish red color, most marked over the malar prominences. The patient complained that in shaving he could not feel the razor and, as he expressed it, his face felt dead.

Examination of the nasal secretions was negative with respect to acid-fast organisms. The blood at this time gave a slight positive reaction (complement binding in the presence of leprosy culture antigen and Wassermann antigen [Noguchi]). It is noteworthy that the semen which was collected at this time by Dr. Harris not only showed acid-fast organisms in the stained preparations but yielded a culture which was subsequently identified as the leprosy bacillus. No specific organism was found though a great number of smear preparations were examined.

On February 4, 1911, the patient was given subcutaneously into the outer side of the left arm four million killed leprosy bacilli suspended in 1 c.c. of normal salt solution. No local or constitutional reaction was occasioned by the injection. One week later a second injection of dead bacilli (four million) was given subcutaneously into the right arm; again no reaction either local or constitutional followed the injection.

At weekly intervals over a period of five months the patient has received subcutaneous inoculations of killed leprosy bacilli in gradually increasing doses until four billion were being administered at a single injection. During the first two months of treatment no local or constitutional symptoms followed the inoculations. After this period, however, reactions were obtained which at first were slight. The reaction at first manifested itself as a mild erythematous patch surrounding the inoculation site, which would persist for two or three days and then disappear. Subsequent injections have given rise to hard, tender inflammatory masses which gradually increase in size and in a week or ten days fluctuate and sometimes rupture, discharging a bloody purulent material. The ulcer after rupture would heal kindly and promptly. Cultures prepared from the fluctuating tumor have in every instance proven sterile. Microscopic examination shows the material to be made up almost entirely of polymorphonuclear leukocytes, many of which are filled with acid-fast bacilli.

At this time the patient's face would appear more rough and swollen and the

macule on the buttock became more elevated and darker red in color. The smears prepared from the serum from this macule now showed great numbers of polymorphonuclear leukocytes and relatively the same number of bacilli as when first examined. From this time on, the skin lesions (face, buttock, and toe) began to subside and in two or four months after the first inoculation had completely disappeared.

After the reaction was obtained it was thought advisable to increase the interval of inoculation to two weeks and cut down the dose. Marked improvement has been noted and felt by the patient from the time the first skin reaction occurred. Gradually the rheumatoid pains disappeared and the patient in four months after the first injection recovered completely the use of his foot. The swollen, purplish color of the face has entirely subsided; the trophic ulcer on the outside of the left little toe also has healed.

The man says that he now feels as well as he ever did in his life and that he can feel the razor when shaving and "life has returned" in his limbs and arms. Clinically and bacteriologically the patient is entirely well. There are no lesions on his body and all signs and symptoms have disappeared.

It is noteworthy that at no time after the treatment was begun did the patient develop any new skin lesions and those present began steadily to retrogress after the first local skin reaction was obtained.

During the course of the treatment repeated examinations of the serum from the incised macule on the buttock were made in order to note the character of the cells and the number and appearance of the bacilli. As the lesion subsided the bacilli became fewer and fewer until at present they are no longer demonstrable. The blood has shown a moderate degree of leukocytosis (11,000 to 13,000—polymorphonuclear leukocytes 70 to 80 per cent) which is most marked in 24 to 48 hours after the injection.

Result of treatment: Apparently cured.

CASE 3. White girl, aged ten years, a native of Louisiana, was admitted to the Home two years ago, having had leprosy for two or three years before admission. On admission to the Home patient presented a characteristic macular eruption bilateral on trunk and limbs and perforating ulcer on one foot. At this time the face was free from eruption, and there was no evidence of distinct tubercles on any part of the skin. Analgesia was well marked in both the upper and lower extremities, one of the lower limbs presenting a scar which was the result of an injury caused by the gnawing of a rat during sleep. Both the ulnar nerves were enlarged. Since admission to the Home the perforating ulcer has healed, but the other symptoms have persisted, and in addition a crop of tubercles has appeared on the face and arms. These nodules at the commencement of the vaccine treatment were about the size of a split pea, unusually non-inflammatory in character, varying in color from a very light brown to a darker shade. They were rounded in outline, distinctly demarkated from the intervening normal skin, cheeks, chin, and ears. Those on the forehead and cheeks were discrete, but on the chin and in the lobes of the ears they were massed together and showed evidences of continuing enlargement. There were about 50 such nodules on the face, and on the forearms about an equal number, distributed on both flexor and extensor surfaces. There was no general infiltration of the skin of the face, and the case was selected for treatment with vaccine because the individual, discrete nodules offered a good opportunity to observe possible effects of treatment, and because from the point of view of its progressions, the disease as affecting the skin was still in its incipiency.

This case was unable to take Chaulmogra oil and was progressing unfavorably under strychnine and Fowler's solution, which was discontinued when the vaccine treatment was commenced.

The first injection of vaccine was made on January 28. The dose was 0.15 c.c. of a vaccine estimated to contain 250 million bacilli per cubic centimeter. One injection a week was given, increasing to 1 c.c of a vaccine containing 800 million bacilli to the cubic centimeter. Two subsequent injections of an equal dose were given at intervals of one week. The vaccine was then temporarily stopped on account of the violence of the reaction both locally and generally. With the first small doses no reaction was observed either local or general, but as the dose was increased, the site of each injection showed the evidences of inflammation which increased in severity until large, hard masses the size of an egg formed at each puncture. These developed into abscesses after running an indolent course of a month or two. The abscesses were allowed to rupture and discharge spontaneously except one which was opened for microscopical examination of the pus contents. The discharge continued for several months and at the present writing (June 25, 1911) the most recent are still unhealed.

No constitutional reaction was observed in this case until several weeks after the last injection. Fever then developed and a curious swelling of the hands and feet. The elevation of temperature ran an irregular course of about one month's duration, the rises and falls resembling septicemia, varying from almost normal to 104° F. The swelling of the hands and feet occurred at the same time. Both hands and feet were enlarged to about one-third more than their natural size. The swelling was non-inflammatory in character, and looked like ordinary edema, but was distinctly hard to the touch, and did not pit on pressure. During the last month this swelling has gradually disappeared until at the present writing the hands and feet have regained their normal size.

Effect of treatment: At the present writing the skin of the face and arms shows a marked improvement. The only distinct nodules are on the chin and ears, where the eruption was most marked before the vaccination. These are now reduced to about half their size and number. The tubercles on the cheeks have almost entirely disappeared, leaving a brownish pigment on their former site. A similar resolution seems to have taken place in the nodules on the arms. No change has been observed in the macular eruption on the trunk and limbs.

CASE 4. White woman, aged 19 years, a native of Louisiana, admitted to the Lepers' Home three years ago, has had leprosy for eight years. Type, mixed. Stage, incipient. The condition of the patient in spite of the duration of the disease was good at the commencement of the vaccine treatment; there was no leonine expression and no claw hand. There was a macular eruption on the trunk and limbs and one slightly infiltrated macule on the cheek, also analgesia of the hand and forearm. There were no tubercles. Treatment was commenced January 28, 1911 with subcutaneous injection of seven minims of vaccine containing 250 million bacilli per cubic centimeter. Weekly injections were continued increasing the dose until March 11, 1911, when thirty minims of vaccine of 800 million per cubic centimeter were given. The local reaction was identical in character with Case 3, but was observed to come on sooner with the larger initial dose. This case also showed a similar swelling of the hands. The constitutional reaction was interesting on account of the severity of the inflammation in the old macules, which occurred during the week of the last injection. The patient was confined to bed for three weeks with temperature ranging from 102 to 103

and intense inflammation in the old lesions on the arms and legs. The legs from the knees upward were involved with an eruption which looked like erysipelas, it was elevated, red, painful; there was also pain in the joints. Exfoliation of the epidermis occurred after the subsidence of the inflammatory symptoms.

Effect of treatment: Macular eruption unchanged on trunk and limbs. Improvement in infiltrated patch in cheek.

CASE 5. White woman, aged 22, a native of Texas, an inmate of the Home for three years, has had leprosy for 11 years. Type, mixed. Stage, advanced. At commencement of vaccine treatment, patient presented the characteristic appearance of leprosy of the advanced skin type, approachnig the terminal stage of the disease. The nerve symptoms were less marked. Besides the general infiltrated macular eruption and leonine facies, the respiration was difficult and speech was possible only in a whisper. The vaccine was given exactly as in other cases. The local reaction was the same as Case 4. One abscess from injection of 600 million bacilli, on February 25, 1911, remains still unhealed.

CASE	TREATMENT	DATE OF INOCULATION	LEUKOCYTE COUNT	
			Before Injection	24 to 48 Hours after Injection
Pablo	8 million killed bacilli injected subcutaneously	July 12, 11	5,600	11,000
Pablo	1 billion killed bacilli injected subcutaneously	July 20, 11	5,790	14,000
Pablo	4 billion killed bacilli injected subcutaneously	August 4, 11	6,000	21,000
Chevalier	4 billion killed bacilli injected subcutaneously	July 1, 11	7,420	12,000
Chevalier	4 billion killed bacilli injected subcutaneously	July 12, 11	8,000	15,000
Chevalier	4 billion killed bacilli injected subcutaneously	July 18, 11	5,000	21,000
Figaro	4 hundred million killed bacilli injected subcutaneously	July 12, 11	8,200	16,000
Figaro	4 billion killed bacilli injected subcutaneously	July 18, 11	5,000	21,000
Figaro	4 billion killed bacilli injected subcutaneously	July 25, 11	6,820	17,000
Smith	1 c.c. protein extract of *B. leprae*	August 14, 11	6,000	15,720
Smith	1 c.c. protein extract of *B. leprae*	August 23, 11	6,280	22,000
Smith	1 c.c. protein extract of *B. leprae*	August 29, 11	7,200	19,300

Four other abscesses have left ulcers at seat of injection which are healing nicely. Patient was confined to bed for one week after last vaccination, with fever and inflammatory symptoms in old tubercles and infiltrated macules. A few tubercles became so violently inflamed that suppuration occurred and small abscesses formed which discharged and healed.

Result of treatment: Up to date of writing, marked improvement has been noted in patient's condition.

CASE 6. White male, aged 18, a native of Louisiana, has had leprosy for 13 years and has been an inmate of the Leper's Home two years. Type of the disease is mixed, with a preponderance of the nerve symptoms. The ulnar nerve is enlarged to about the size of a man's little finger. His face and ears are covered with tubercles and infiltrated patches. The length of time that elapsed after the last injection, before any constitutional symptoms appeared, was three weeks. The temperature rose to 104° F. and the inflammatory evidences in old tubercles was characterized by pain. Marked improvement has been noted in patient's condition as a result of treatment up to present date.

DISCUSSION AND SUMMARY.

If our explanation of the factors underlying infectibility of animals by the leprosy bacillus is correct, we must assume that the epithelioid cell is more or less essential to the growth of the bacterium. Among human cases, however, it is evident that, even though these cells may be necessary in order that the bacilli can proliferate, contrary to our experience with animals, the microorganism appears able under ordinary conditions to prolong indefinitely its vitality in the human tissues. Such being the case, there remain but two methods by which we may hope to eradicate the disease; either the bacilli situated focally must be walled off, as frequently occurs in tubercle infection, or the host conditions must be so altered that the bacilli will be unable to live. The former process is at best unsatisfactory and appears almost impossible of procuring, as leprous lesions disclose little tendency toward fibrous tissue encapsulation. There remains, therefore, but the possibility of altering conditions, which theoretically can be procured either by the development of substances in the body fluids inimicable to the growth of the organism, that is, the commonly appreciated immune bodies, or the stimulation of cells which are capable of destroying the bacilli by phagocytosis. Since the production of the development of immune bodies is comparatively inadequate it would seem that only by phagocytosis can the bacilli be destroyed.

It is apparent that the epithelioid type of cells (including the lymphoid and plasma cell) is comparatively useless as a destructive agent, if not positively helpful to the growth of the bacterium. On the other hand, there is every proof that the polymorphonuclear leukocyte is capable of destroying the leprosy bacillus in a manner similar to that in which it destroys the pyogenic cocci, etc. We

find that although such cells are usually present in small numbers in human leprous lesions, only infrequently are many found.

Since both the leprosy bacillus and the disease of leprosy have many points in common with the tubercle bacillus and tuberculosis respectively, it is justifiable to discuss in this paper phenomena noted in the latter disease. Our experience suggests, moreover, that certain conditions which are of interest and importance in the study of tuberculosis are exemplified by observations upon experimental leprosy, more particularly, the reactions of a focal character and the subsequent changes in the lesions which follow the inoculation of dead bacilli or the bacterio-protein.

The bacillary products of *B. leprae* like those of *B. tuberculosis* are relatively non-toxic in the ordinary sense of this term; they will not readily poison a normal animal (enormous doses in relation to body weight being necessary) nor will they stimulate antibodies in the host in amounts directly proportionate to the quantity of "leprosin" introduced.

In view of the difficulty experienced in the production of a protective immunity against the tubercle bacillus and the comparative absence of agglutinins, opsonins, amboceptors, etc., in the serum of animals and patients recovering from or cured of an infection by the tubercle bacillus, numerous theories have been brought forward to explain the cure of this disease.

Baldwin[1] believes that in the employment of tuberculin in the treatment of tuberculosis two factors are important, namely, immune-body production and reactive inflammation at the site of the individual lesions. This author makes, however, no attempt to explain why the focal reaction takes place nor the manner in which it influences favorably the subsequent course of the disease.

Recently[2] Krause in an article based upon experimental as well as human studies of immunity to tuberculosis states as his opinion that the ordinary tuberculin reaction in animals and in patients is, perhaps, due to the absorption of toxic material from the lesions irritated as the result of injection rather than due to the toxicity of the material inoculated. Further, he writes: "Since we know that tuberculo-protein inflames the tubercle it is more than likely that the end result of every dose, no matter how slight, is to bring about changes that may vary from the most transient hyperemia to the most intense inflammation of the focus. The purpose of such changes would be, of course, conservative and their end would be fibrosis." He likens tuberculin treatment to the employment of silver nitrate, copper sulphate, etc., in the treatment of chronic ulcers.

[1] *Jour. Med. Res.*, 1910, 22, p. 189. [2] *Ibid.*, 1911, 24, p. 3.

Krause's observations we believe represent the most modern and apparently the most correct view relative to the method of action of tuberculin in the therapy of tuberculosis. Our experience in dealing with the products of *B. leprae* is in accord with his regarding the function of tuberculin. Since, however, we have in leprosy a disease which is characterized by less danger from toxic reactions, it is justifiable to employ more heroic measures in the treatment of this disease than in tuberculosis. Furthermore, leprosy offers a better opportunity than tuberculosis for the study of the immunity principles underlying both infections. In order, however, to explain the phenomena occurring in the process of infection and cure of such diseases as tuberculosis and leprosy, it appears that some theory more elaborate than those commonly considered must be conceived.

The following appears to us to present a working hypothesis concerning the changes taking place within the body following the administration of a dose of leprous protein. As stated above, it appears that the growth of the bacilli continues normally because the organisms themselves are of the nature of non-irritating foreign bodies which proliferate within cells of the epithelioid type. It is probable that there constantly takes place a splitting of certain numbers of bacilli with the freeing of toxic products; usually, however, the anti-anaphylactic bodies directed against these toxic substances are present in sufficient quantity to render them at once inocuous, in other words, the absence of cellular (polymorphonuclear) and febrile reaction is due to a balance having been established between the bodies. By means of the subcutaneous injection of leprous protein a comparatively large amount of toxic body is liberated as the material is at once brought into contact with the body fluids. As a result of this increase in toxic products there is a withdrawal to the spot of the available antitoxic body. When this occurs any splitting of leprosy bacilli situated focally will result in the bacilli in these areas acting as toxic bodies of sufficient potency to determine the accumulation of polymorphonuclear leukocytes following perhaps their liberation from the epithelioid cells as the result of the destruction of the latter by the toxin. Thus would be brought to bear upon the bacilli whatever immune bodies were present in the body fluids owing to the loss on the part of the

bacilli of the protection of the epithelioid cells as well as the destructive properties of the pus cells.

It is comparatively easy to understand why, in an individual in whom there is a balance of split protein and antisplit protein bodies, the introduction of material in such a manner that it is liable to rapid splitting into toxic molecules should result at the point of inoculation in a constitutional disturbance and in a local reaction. Why, however, such an inoculation should result in focal reactions at the sites of infection is much less readily understood. For the present we can see no hypothesis which explains this phenomenon other than the disruption of the balance between toxic split protein and the antibody of such material. If we consider that as a result of this lack of balance each individual lesion becomes a toxic focus we can conceive of the factors determining the occurrence of hyperemia and the presence of leukocytes.

It is well known that sterile soluble or insoluble material, such as catgut, silk, or many of the metals imbedded in the tissues, do not attract pus cells. If, however, the catgut or silk be saturated with turpentine or croton oil an abscess develops. In a similar manner it seems that leprosy bacilli ordinarily act upon the tissue much as sterile catgut, etc., but that under certain conditions they act as irritants of sufficient activity to lead to the accumulation of pus cells. Experimental evidence proves that the acquired irritability is of the nature of an anaphylactic or allergic toxicity acting in a matter similar to that just described.

The chronicity of leprosy, which is one of the most marked characteristics of the disease, might be accounted for by the fact that the protein content of the casual agent is not readily split and in consequence there is apparently no reaction on the part of the host which is sufficiently potent to cause destruction of the bacilli. As a result of this lack of toxicity the reactive forces of a useful type are not developed.

This view is similar in many respects to von Pirquet's explanation of the apparent immunity of individuals previously infected by diseases such as vaccinia, smallpox, etc., namely, that the freedom of such persons from subsequent infection is not based upon an acquired insensibility against the virus causing the disease, but to

an early reaction taking place upon the introduction of the causative agent.

Such an explanation of the apparent immunity of individuals who have recovered from infection by one or other of the exanthemata is satisfactory to a certain degree, but explains insufficiently the focal reactions which occur in both tuberculosis and leprosy. We believe that the local allergic reaction of von Pirquet and the focal reactions at the site of the lesions can be better explained by considering that as the result of a hypersensitive or anaphylactic state the virus or protein substance which, to the normal person, is non-toxic and therefore causes no local irritation and hence excites no reaction is at once split into a toxic substance by the previously manufactured toxic bodies. As a result of the rapid freeing of toxines a reaction of greater or less intensity at once ensues, resulting in the destruction of the invading virus. According to our conception, the reaction is the result, not of the death of the organism through its binding with the antibody, but of the split protein-toxic body, and the reaction by means of the cells involved brings about the death of the virus.

The phenomenon of acute exacerbation of the leprous lesions occurring from time to time during the course of the disease accompanied by fever is well known. It has also been noted by clinical observers that following attacks of fever the lesions which have been involved in the more active process have a tendency to disappear. It has been pointed out, moreover, that the increased redness, swelling, and pain in the lesions are accompanied by all the microscopic evidences of an acute inflammatory reaction, including large numbers of polymorphonuclear leukocytes. Therefore the reactions obtained in the human leper by the injection of dead bacilli are analogous to those which develop naturally in certain cases (so-called lepra fever). Our results justify also the belief that the same satisfactory end result is obtained, namely, improvement in the lesions involved in the acute reaction. Since we are in a position to control by inoculations the severity and extent of the reactions both local and constitutional, it appears that we have at our disposal a means of permanently and markedly ameliorating the condition of the leper.

In the treatment of leprosy with killed cultures of the bacilli,

whether the whole bacilli or the extracted proteins are used it would seem essential to give large doses and often repeated, at least until the local anaphylactic reaction appears. The dose should be not less than 400 million and should be increased gradually at weekly intervals until a marked local reaction is obtained, at which time the number of killed bacilli administered is three to eight billions, or the equivalent of this number if the protein is used. In some cases the local reaction occurs after the third or fourth injection; in others not until 15 or 20 injections have been given. Once this reaction develops, the dose may be lessened and the interval between administration increased. We have followed the plan of administering subsequent injections as soon as the local reaction and leukocytosis following the previous injection have subsided.

A careful study of the blood changes during the course of treatment is important, as the rise and fall of the polymorphonuclear leukocytes is a most excellent control of the dose to be given and the intervals to observe between injections. We have found that there is induced a marked leukocytosis after each injection which diminishes *pari passu* with the subsidence of the local reaction, the period of recrudescence varying from three days to two weeks, depending on conditions. Therefore, at the time of subsidence of the leukocytosis (see table), another dose should be given if the best results are to be obtained.

Whereas, in the treatment of tuberculosis anything but minute doses is liable to do serious harm, large doses of the specific bacterioprotein in the treatment of leprosy can be employed with impunity. In fact, leprosin must be given in large doses and often repeated if beneficial results are to accrue. In other words, leprosin, unlike tuberculin, can be pushed to the limit.

In none of the cases treated by us have new lesions developed after the local reaction was obtained. In early cases there is a complete subsidence of all visible lesions and other signs of the disease in four to six months after systematic treatment has been begun and carried out. We believe, therefore, that the proper administration of the product of *B. leprae*, whether the protein extract or the whole killed bacilli are used, will not only ameliorate the condition of the leper but in early cases, including both types of the disease, will bring about a permanent cure.